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Early detection of breast cancer depends on the accurate classification of microcalcifications. We have developed a computer vision system that can classify microcalcifications objectively and consistently to aid radiologists in the diagnosis of breast cancer.

A convolution neural network (CNN) was employed to classify benign and malignant microcalcifications in the radiographs of pathological specimen. Digital images were acquired by digitizing radiographs at a high resolution of 21 μm x 21 μm. Eighty regions of interest selected from digitized radiographs of pathological specimen were used for the training and testing of the neural network system. The CNN achieved an A_z value of 0.90 in classifying clusters of microcalcifications associated with benign and malignant processes.

The classification of microcalcifications for the diagnosis of breast cancer was achieved at a high level in our computer vision system that consists of high resolution digitization of mammograms and a CNN. We have demonstrated the great potential of CNN in classification of microcalcifications for diagnosis of breast cancer.

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Introduction

Breast cancer is one of the leading causes of death among women. However, there is clear evidence that early diagnosis and subsequent treatment can significantly improve the chance of survival for patients with breast cancer.[1 - 4]

Mammography has become one of the major diagnostic procedures with a proven capability for detecting early-stage, clinically occult breast cancers.[5 - 8] However, breast cancers in their early stage are small and frequently their radiographic appearance differs only subtly from that of normal tissue or benign abnormalities. Because of this subtlety, the potential for misclassification by radiologists is substantial. Only 10-30% of cases that have mammographically suspicious findings and are subjected to biopsy prove to be malignant.[9] On the other hand, approximately 10-30% of patients with breast cancer are misdiagnosed by mammography (have the cancer missed or not detected on their mammograms).[10-14]

Besides the subtle nature of radiographic lesions associated with breast cancer, many errors in radiological diagnoses can be attributed to human factors such as subjective or varying decision criteria, distraction by other image features, and simple oversight.[15-17] Studies suggest that these errors may occur even with experienced radiologists.[18,19] These errors may be reduced by the use of automated detection schemes that can locate and classify possible lesions, thereby alerting the radiologist to examine these areas with particular caution. Moreover, the automated detection schemes can serve as a "second radiologist", similar to the double reading by two radiologists that is commonly practiced in diagnostic radiology to increase diagnostic efficacy.

Microcalcifications are commonly considered to be important signs of breast cancer. It has been reported that 30-50% of breast cancers detected radiographically demonstrate microcalcifications on mammograms.[20-25] Up to 90% of cases of ductal carcinoma in situ present with microcalcifications.[26] The correlation between the presence of microcalcifications and the presence of breast cancer suggests that accurate detection of microcalcifications will improve the efficacy of mammography as a diagnostic procedure.

Microcalcifications occur in malignant and benign conditions. Some microcalcifications are characteristically benign or are associated with a benign process. For example, calcified fibroadenomas have a typical "popcorn" configuration appearing coarse and solitary. Milk of calcium demonstrates sedimentation.[27] Vascular calcifications have a tram track appearance, typical of vascular calcifications seen in other areas of the body. Dermal calcifications tend to be smooth and round with lucent centers. Secretory calcifications are thick, smooth, cigar-shaped, and usually non-branching. Features supporting benignity include uniform size and density of the calcium flecks, as is seen in sclerosing adenosis.[28] Furthermore, benign microcalcifications tend to be uniformly dense or scattered, without a segmental or linear distribution.[29]

Some microcalcifications associated with malignancy have a typically granular or linear appearance. They usually occur in clusters consisting of greater than 15 particles.[30] The particle size is small (less than 1 mm) and the shape is irregular.[31] Some clusters of microcalcifications have neither the typically benign nor typically malignant configurations described above. These "indeterminate" microcalcifications present a significant diagnostic problem and require careful analysis.

The number of microcalcifications per cm^2 has been shown to be the most important predictor of malignancy, with clusters consisting of less than 10 microcalcifications per cm^2 having a high chance of benignity. Clusters consisting of microcalcifications numbering greater than 15 per cm^2 have a higher chance of malignancy.[32]

The task of detection and classification of microcalcifications for the diagnosis of breast cancer is a difficult one. The inability to correctly predict cancer is not only due to the overlap in appearance between microcalcifications associated with benign and malignant conditions, dense breasts, improper technical factors or simple oversight by radiologists may contribute to the failure to detect microcalcifications. Differing levels of confidence and training among interpreting radiologists may lead to inconsistent recommendations for management.

Radiologists classify breast microcalcifications into one of three groups: benign, likely malignant, and indeterminate. Most patients with indeterminate

types of calcifications undergo a breast biopsy to exclude cancer. Any method that would correctly classify benign types of calcifications previously considered indeterminate would decrease the frequency of biopsy and therefore the cost of detection of breast cancer.

Several investigators have been developing computer programs for the automated detection of microcalcifications on mammograms.[33-36] Chan *et al.* showed that the computer program can detect subtle microcalcifications that may be missed by radiologists, indicating that it is a promising approach to the automated detection of microcalcifications.[37] More recently, Wu *et al.* applied an artificial neural network (ANN) to detect microcalcifications.[38] The ANN, trained by using the power spectrum of regions of interests (ROI) containing microcalcifications, was able to eliminate 50% of false-positive detections of a rule-based scheme[37,39] while preserving more than 95% of the true-positive detections. The neural network achieved an A_z value of 0.85 for the detection of clustered microcalcifications. Several other computer schemes for detection of microcalcifications were also reported by Astley *et al.*,[40] based on likelihood estimators, by Grimaud *et al.*,[41] using mathematical morphology tools, and by Karssemeijer,[42] using a stochastic method based on Bayesian decision theory.

As stated earlier, microcalcifications can be associated with either benign or malignant processes. It is important to distinguish different types of microcalcifications after they have been identified by a detection scheme. Accurate classification of microcalcifications into benign and malignant groups would help improve the sensitivity of the diagnosis as well as reduce the number of unnecessary biopsies.

As the first step in the process of developing an automated computer scheme for classification of microcalcifications, a neural network system was developed to classify microcalcifications in the radiographs of biopsy specimens. Classification of microcalcifications in radiographs of biopsy specimens is an "idealized" situation.

In biopsy specimens, underlying tissue around microcalcifications is less than that present in normal mammograms. Therefore, the scatter radiation recorded on films is reduced, resulting in improved contrast. Higher dose and geometrical magnification can also be used to obtain radiographs of biopsy

specimens as compared with regular mammograms. Less magnification results in less geometrical unsharpness. Higher exposure can be used to achieve greater signal to noise ratio and thereby improve image quality of radiographs.

Therefore, microcalcifications in the radiographs of biopsy specimens are more clearly represented than those in regular mammograms. After we can successfully apply our algorithm to classify microcalcifications in radiographs of specimens, we will make necessary adjustments to apply the algorithm to the regular mammograms.

In recent years, rapid progress of research on artificial neural networks (ANN)[43] has been reported extensively in the field of computer science and many applied fields. Neural networks address detection, classification, and decision-making problems not by pre-specified "conventional" algorithms, but rather by "learning" from examples presented repeatedly. The popularity of neural networks is primarily due to their apparent ability to make decisions and draw conclusions when presented with complex, noisy, or partial information and to adapt their behavior to the properties of the training data. Neural networks are capable of parallel-processing a large amount of information simultaneously and have been shown[44,45] to be a useful tool for pattern recognition in fields where conventional algorithmic approaches and rule-based expert systems may not be successful.

Methods

The overall approach for the classification of microcalcifications using a CNN system is shown in Fig. 1. The radiographs of pathological specimen are digitized by a high resolution digitizer. Regions of interest (ROI) containing microcalcifications are manually selected. These ROIs are preprocessed and used as input to the CNN system. Finally, the classification results are examined by the ROC analysis.

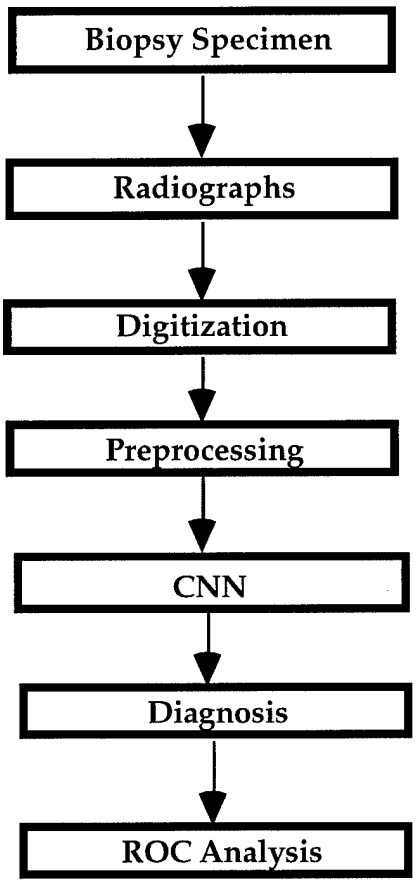


Figure 1. Overall approach for the classification of microcalcifications using CNN.

The classification of microcalcifications is based primarily on the fact that microcalcifications associated with malignant processes generally have more irregular shapes with fuzzy and spiculated boundaries and are less uniform in density and size. They are usually grouped into multi-particle clusters. The microcalcifications associated with benign processes, on the other hand, usually tend to have smoother and well-defined boundaries, rounded shape, and

uniform densities and sizes. The neural network system will be trained to recognize the characteristics of each type of microcalcifications.

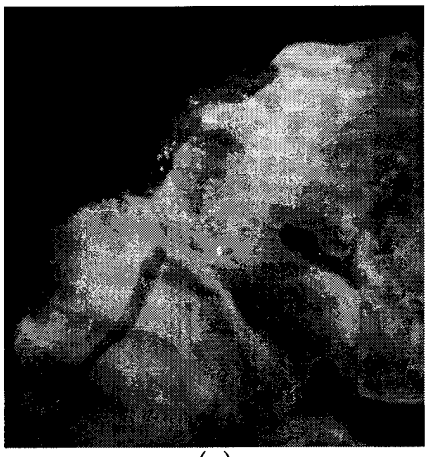
The CNN is based on the network structure of Fukushima's Neocognitron[46] which is designed to simulate the vision of vertebrate animals. The structure of CNN used in this study resembles a simplified Neocognitron. A two-dimensional convolution operation from the input layer to the hidden layer is employed to simulate radiologists' viewing of a suspected area. The CNN has the ability to process and recognize two dimensional image patterns and has been shown to be an effective tool in image processing and pattern recognition.[47-49]

ACQUISITION OF MAMMOGRAMS

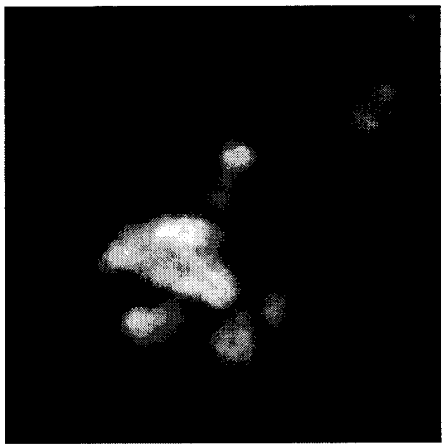
The selected radiographs of breast biopsy specimen are digitized with an image resolution of 21μm x 21μm per pixel by a CCD camera digitizer (DBA Systems Inc.). With high resolution digitization, the morphological information of microcalcifications can be preserved, which enables the neural network system to differentiate different types of microcalcifications on the basis of their geometrical shapes and density patterns. Figure 2(a) shows a cluster of microcalcifications in original radiographs of pathological specimen. Shown in Fig. 2(b) are clustered microcalcifications after being digitized with the high resolution digitizer. The shapes and density patterns of the microcalcifications are better defined in Fig. 2(b) than those shown in Fig. 2(a).

DATABASE

Eighty regions of interest (ROI) that contain clustered microcalcifications (40 benign and 40 malignant) are selected from 60 digitized radiographs of pathological specimen in this study. Figure 3 shows all of the 80 ROIs selected in the database. There are substantial variations in size among benign or malignant microcalcifications. The information concerning the classification of microcalcifications ("truth") are obtained from the results of biopsy examination. Background trend correction is employed to remove the non-uniform background structure in different ROIs.



(a)

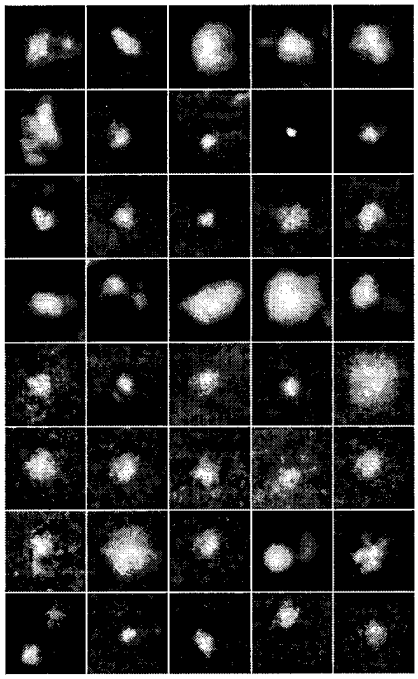


(b)

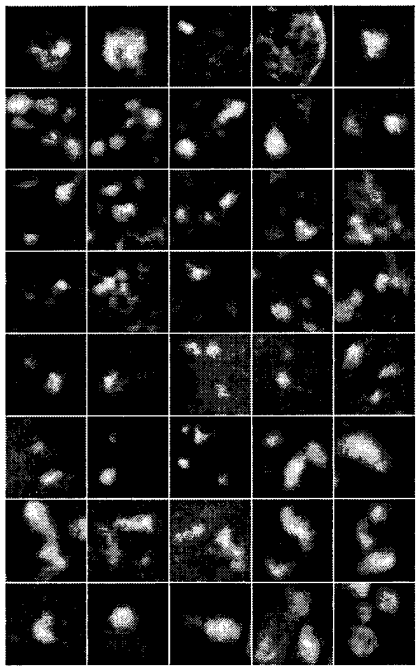
Figure 2. Microcalcifications shown in an original radiograph of pathological specimen (a) and shown in a radiograph digitized with a high resolution (21 μm x 21 μm) digitizer (b).

CONVOLUTION NEURAL NETWORK

The structure of the CNN[47] is shown in Fig. 4. The input to the CNN are ROIs of matrix size of 64 x 64 pixels, containing benign or malignant type of microcalcifications. Only one hidden layer is used in this study. The connections between input and hidden layer are grouped into seven different kernels based on the structure of Fukushima's neocognitron.[46,50] There are two output units in the output layer, with each unit corresponding to a benign or malignant class of microcalcifications. The hidden layer and the output layers are fully connected.



(a)



(b)

Figure 3. Database for the training and testing of the CNN; (a) 40 ROIs containing benign clustered microcalcifications and (b) 40 ROIs containing malignant clustered microcalcifications.

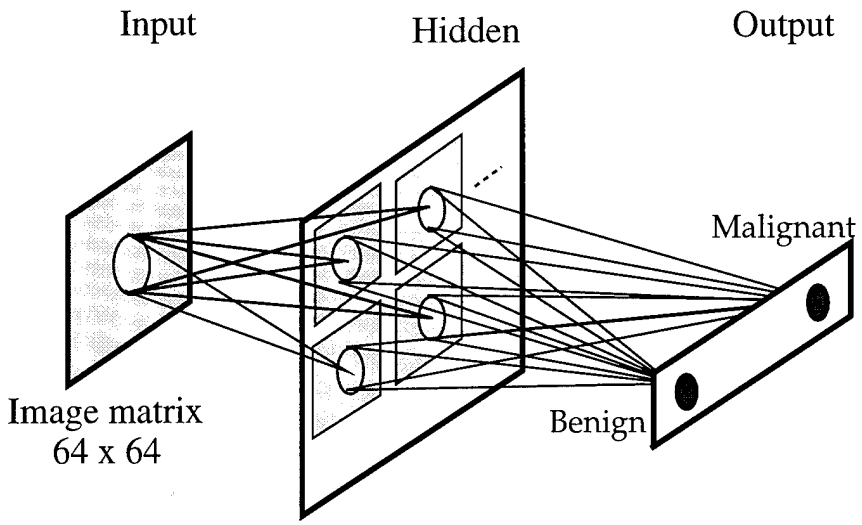


Figure 4. Structure of a convolution neural network used for the classification of microcalcifications.

The training algorithm of the CNN is similar to that of a backpropagation neural network, in which backpropagation and the generalized delta rule are used in the training process.[51] The input signals are now two dimensional images. The weights are all arranged in the convolution kernels. In the feed-forward propagation, the output of *l*th layer are first convoluted with weight filters. The sum of the convolution is then added by a bias term to form the net input to the next layer.

$$N_q^{l+1}(x,y) = \sum_{p=1}^{P^l} [O_p^l * W_{p,q}^l]_{(x,y)} + b_q^{l+1} \qquad [1]$$

where $N_p^{l+1}(x,y)$ is the net input to the unit (x,y) in layer $l+1$, $O_p^l(x,y)$ is the output of the unit in layer l, $W_{p,q}^l(x,y)$ is a weight kernel, and b_q^{l+1} is a bias term in layer $l+1$. In the notation, layer number l = (1, 2, ..., L), cluster number in the lth layer p = (1, 2, ..., P^l), and cluster number in the ($l+1$)th layer q = (1, 2, ..., P^{l+1}). Note that $*$ denotes discrete convolution,

$$[O_p^l * W_{p,q}^l]_{(x,y)} = \sum_i \sum_j (O_p^l(i,j) \cdot W_{p,q}^l(i-x, j-y)). \qquad [2]$$

We can then rewrite equation [1] as

$$O_q^{l+1}(x,y) = f(N_q^{l+1}(x,y)), \qquad [3]$$

where f is the activation function

$$f(x) = \frac{1}{1+\exp(-x)}. \qquad [4]$$

In the error backpropagation, the weights are modified, similar to that in Eqn.[2], as the following,

$$\Delta W^{l}_{p,q}(n+1) = \eta(d^{l+1}_{q} * O^{l}_{p}) + \alpha \Delta W^{l}_{p,q}(n), \qquad [5]$$

to minimize the error function,

$$E = \frac{1}{2}\sum (T(x,y) - O^{L}_{1}(x,y))^2, \qquad [6]$$

where $T(x,y)$ is the target output.

In the training process of the CNN, each image block is rotated and reflected such that the number of training data are increased eight fold. The rotation and reflection represent different orientations of microcalcifications in mammograms. The training with additional orientation can effectively make the CNN rotational invariant.

Results

JACKKNIFE METHOD

A jackknife method was employed to evaluate the performance of the CNN. In the jackknife method, half of the ROIs were randomly selected from the database of 80 ROIs. These ROIs were used to train the convolution neural network. The other half of the ROIs were then used to test the performance of the CNN. By choosing different random samples from the database, the jackknife test can be repeated to generate multiple test output and provide a better estimate of the true performance of the CNN in classifying benign and malignant clusters of microcalcifications.

ROC ANALYSIS

The output values from the two output units were examined by using Receiver Operating Characteristic (ROC) analysis.[52,53] The LABROC4 algorithm[54] developed by Metz *et al.* was used to fit ROC curves to the continuous data from the output of CNN. The area under the ROC curve (A_z) was used as an overall measure of diagnostic performance. The result from each jackknife test was analyzed individually by using ROC analysis. Ten jackknife tests were performed. A final ROC curve was obtained by averaging the results from the 10 jackknife tests, as shown in Fig. 5. The CNN system performed very well in classifying benign and malignant clusters of microcalcifications, achieving an A_z value of 0.90.

POTENTIAL APPLICATION IN RECOMMENDING COURSES OF ACTION

A potential application of CNN is to classify microcalcifications into groups of definitely benign and possibly malignant. By applying a low threshold level to the output values of the CNN, we can make CNN a classifier that is not very specific but with 100% sensitivity.

With such a classifier, some benign microcalcifications may be classified as possibly malignant, but all of the microcalcifications classified as benign are definitely negative. Thus, radiologists can ignore the clusters of

microcalcifications that are classified as benign and only concentrate on those that are classified as possibly malignant. As a result, the time radiologists spend reading mammograms can be reduced and detection efficacy of breast cancer can be expected to improve.

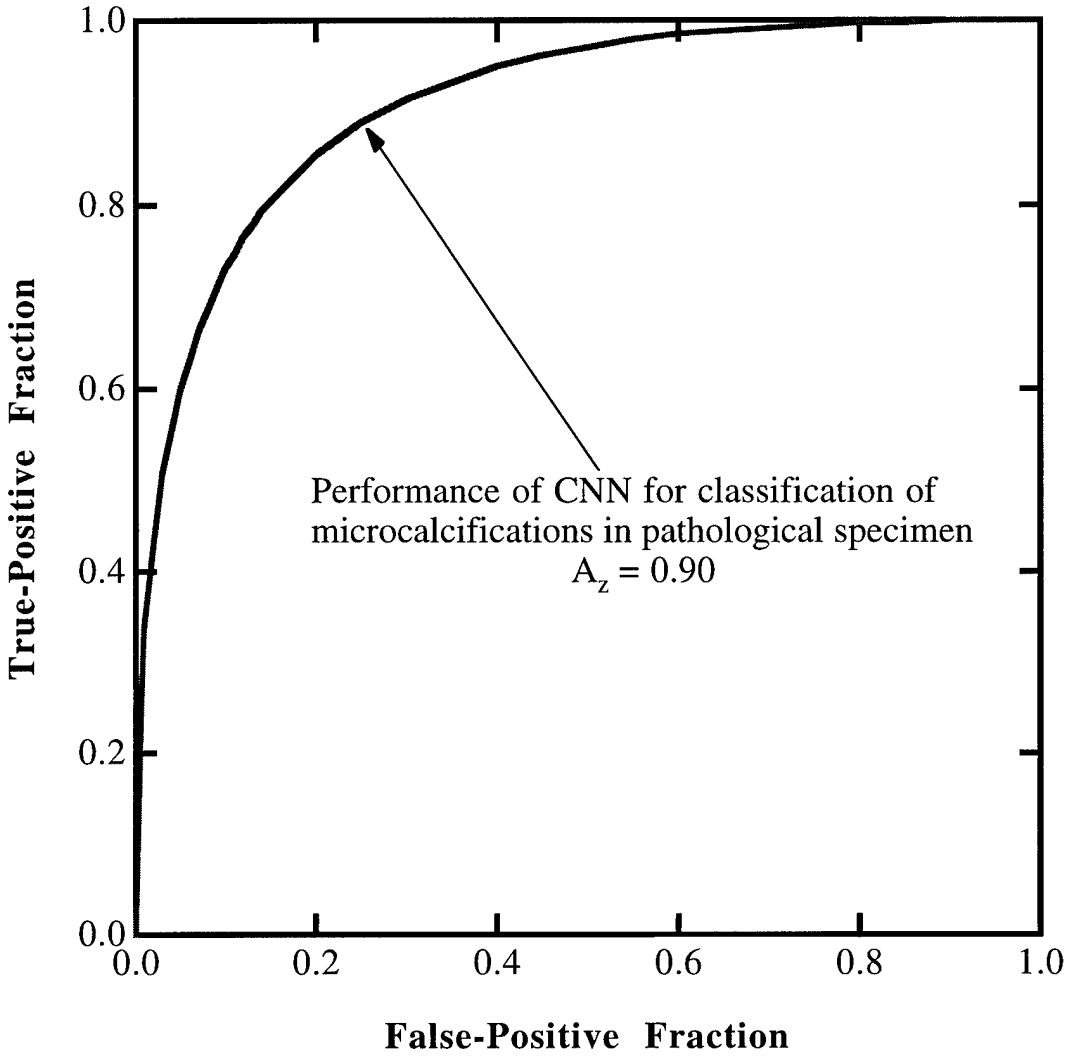


Figure 5. ROC analysis of the performance of CNN in classifying benign and malignant microcalcifications.

The ability of CNN to serve as a classifier to eliminate benign microcalcifications can be demonstrated in Table I. In each of the jackknife tests, we set threshold levels of the output of CNN such that all of the malignant ROIs are to be called positive by the computer system and calculate the number of the

benign ROIs that can be called negative (i.e., have output values below the threshold level for positive ROIs).

Table I shows the results for each individual jackknife test as well as the averaged results of the 10 jackknife tests (second column). The CNN can identify, on average, approximately 42% of the benign clusters of microcalcifications with 100% sensitivity (without missing any malignant clusters). Therefore, if this CNN system were used to help radiologists in detecting malignant microcalcifications, radiologists would only need to examine about half of the detected microcalcifications.

As discussed earlier, studies have shown that approximately 10-30% of breast cancers are missed by mammography and only 10-30% of biopsy cases recommended by mammography are actually malignant. As a comparison to the reported performance of radiologists in breast cancer diagnosis, we also listed in Table I (third and fourth columns) the average specificities and positive predictive values, defined as the portion of malignant cases among the biopsied cases.

With a sensitivity of 80%, approximately the same level of sensitivity reported by average radiologists, the neural network system achieved a positive predictive value for malignancy of 84%, compared with 10-30% achieved by radiologists. Therefore, the CNN appears to be a very promising tool for assisting radiologists in making decisions for the diagnosis of breast cancer.

Discussions

It is important to note that the CNN is designed as an automated classifier of microcalcifications for the diagnosis of breast cancer. It will be used in conjunction with other schemes for the detection of microcalcifications in digital mammograms. Once microcalcifications are detected, the CNN will be applied to classify them into benign (negative) and malignant (positive) groups. Radiologists can ignore the microcalcifications that are classified into the benign group and examine those that are classified as malignant to decide whether to recommend biopsy or short term follow-up exams.

TABLE I. APPLICATION OF CNN IN RECOMMENDING COURSES OF ACTION

Jackknife Test	Correctly identified negative cases at 100% sensitivity	False Positives at 90% sensitivity	False Positives at 80% sensitivity
1	16	2	2
2	12	7	2
3	15	2	0
4	2	6	6
5	11	3	1
6	4	2	2
7	7	4	2
8	7	8	8
9	3	5	5
10	6	5	2
Average	8.3	4.4	3
Average Specificity	42%	78%	85%
Positive Predictive Value*	63%	80%	84%

** Positive Predictive Value — Defined as the portion of the actually positive cases among the cases diagnosed that are classified as positive by a diagnostic system.*

The results discussed are based on radiographs of biopsy specimen of microcalcifications. The specimen images have, in general, better image quality and greater signal-to-noise ratio than the regular mammograms. The radiographs digitized with high resolution digitizers provide the morphological information of individual microcalcifications that makes the classification of microcalcifications into benign and malignant groups possible. The CNN system will need to be tested on regular mammograms. Some parameters of CNN may need to be fine tuned when applied to regular mammograms and the CNN system may not achieve the same performance level as it did in this study.

Both a large training and testing database are necessary in order to train and evaluate the performance of the neural network sufficiently and reliably. We will be expanding our database significantly in the future. To further improve the accuracy of the classification, a hybrid neural network (HNN)[55] will also be employed to classify microcalcifications based on the input of both image data and image features[56] that will be automatically extracted.

Conclusions

We have demonstrated that the convolution neural networks can be an effective tool in the diagnosis of breast cancer. The results obtained in this study are very promising, even though they were based on a relatively small training and testing database. These results indicate the potential usefulness of CNN in classification of microcalcifications in digital mammograms. An extensive clinical test of our developed system using real mammograms will be needed to determine the clinical applicability.

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Appendix

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